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EXAMINER	
ROARK, JESSICA H	
ART UNIT	**PAPER NUMBER**
1644	10

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application N . 09/643,595	Applicant(s) BARBERA-GUILLEM ET AL.	
	Examin r Jessica H. Roark	Art Unit 1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 September 2001 and 11 April 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-17* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *22 August 2000* is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

RESPONSE TO APPLICANT'S AMENDMENT

1. Applicant's amendment, filed 4/11/02 (Paper No. 7), is acknowledged.
Claims 1-2, 4-7, 9-11, 13-15 and 17 have been amended.
Claims 1-17 are pending and are under consideration in the instant application.

2. This Office Action will be in response to applicant's arguments, filed 9/24/01 (Paper No. 4).
The rejections of record can be found in the previous Office Action (Paper No. 3).

It is noted that New Grounds of Rejection are set forth herein.

3. Applicant's amendment, filed 4/11/02, has obviated the previous rejections of claims 2, 5, 7, 9, 11, 13-15 and 17 under 35 U.S.C. 112, second paragraph.

4. Claims 1-2, 4-7, 9-11, 13-15 and 17 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one of ordinary skill in the art that the inventor, at the time the application was filed, had possession of the claimed invention. The following *written description* rejection is set forth herein.

The instant claims are drawn to a method for reducing a pro-MS immune response and treating MS by administering an "affinity ligand" which selectively binds to a B cell determinant and can be administered in an amount effective to deplete B cell.

The specification discloses that an "affinity ligand" is any molecule which has binding specificity and avidity for a determinant associated with a B cell (e.g., page 13, 3rd paragraph). Thus the genus of molecules encompassed by the term "affinity ligand" is very large, and is based solely upon a function shared by the members. The specification also discloses that an "affinity ligand" may be a lectin, an antibody, a peptide, or an aptamer (see bridging paragraph of pages 13-14).

Applicant has not disclosed, nor does the art recognize, the requisite structural features of the genus of "affinity ligands" which function to bind a B cell determinant and can be administered in an amount sufficient to deplete B cells, a feature deemed essential to the instant invention. The level of knowledge and skill in the art would not permit the artisan at the time of the invention to envisage the methods using a representative number of "affinity ligands" as claimed. Therefore, one of skill in the art would not recognize the Applicants to be in possession of the genus of "affinity ligands" which bind a B cell determinant and can be administered in an amount sufficient to deplete B cells as encompassed by the claimed invention.

Consequently, Applicant was not in possession of the instant claimed invention. See Regents of the University of California v. Eli Lilly and Co. 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997). Adequate written description of genetic material "'requires a precise definition, such as by structure, formula, chemical name, or physical properties,' not a mere wish or plan for obtaining the claimed chemical invention." Id. 43 USPQ2d at 1404 (quoting Fiers, 984 F.2d at 1171, 25 USPQ2d at 1606). The disclosure must allow one skilled in the art to visualize or recognize the identity of the subject matter of the claim. Id. 43 USPQ2d at 1406. A description of what the genetic material does, rather than of what it is, does not suffice. Id.

Applicant is also directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

The Examiner notes that the specification discloses several examples of antibodies which bind a B cell determinant and can be administered in an amount sufficient to deplete B cells (see page 15, middle). Thus claims limited to an affinity ligand that is an antibody would be considered to be supported with an adequate written description in the specification as filed.

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) do not apply to the examination of this application as the application being examined was not (1) filed on or after November 29, 2000, or (2) voluntarily published under 35 U.S.C. 122(b). Therefore, this application is examined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

6. The previous rejection of claim 1-2, 4-5, 10-11, 13-15 and 17 under 35 U.S.C. 102(b) as being anticipated by Bhat et al. (US Pat No. 5,593,676, IDS) is withdrawn in view of Applicant's convincing argument's, filed 9/24/01, that Bhat et al. do not teach a B cell component contributes to the pathogenesis of MS.

7. Claims 1-2, 4-5, 10-11, 13-15 and 17 are rejected under 35 U.S.C. 102(e) as being anticipated by Hale et al (US Pat. No. 6,120,766, see entire document).

Hale et al. teach and claims a method of treating multiple sclerosis (MS) by administering an antibody to the CDw52 antigen (see entire document, including claims). Hale et al. teach that CDw52 is a B cell determinant expressed on human B cells, and that antibody to CDw52 lyses (i.e., depletes) B cells (e.g., column 1, especially lines 35-45). Hale et al. teach that the anti-CDw52 antibody is administered as a composition comprising a pharmaceutically acceptable carrier (e.g., column 2 at lines 57-65), and that the composition may also comprise other drugs conventionally used to treat MS, including the anti-inflammatory agent methylprednisolone (see e.g., column 3 at lines 5-12). Hale et al. teach that the compositions comprising the anti-CDw52 antibody may be administered intravenously, or by other parenteral routes (e.g., column 3 at lines 1-4).

Lysing B cells with an anti-CDw52 antibody *in vivo* would also inherently deplete mature and memory B cells, $CD19^+sTn^+$ B cells, $CD19^+CD21^+sTn^+$ B cells and $CD19^+CD5^+sTn^+$ B cells, including nonmalignant B cells. Finally, administering an anti-CDw52 antibody to treat an individual suffering from MS would also inherently require that the antibody be administered in an amount effective to reduce the inflammation underlying the clinical manifestations of MS. Applicant is reminded that no more of the reference is required than that it sets forth the substance of the invention. The claimed functional limitations would be inherent properties of a method comprising administering an anti-CDw52 antibody to an individual suffering from MS.

An individual suffering from multiple sclerosis would inherently have a pro-MS immune response, as defined on pages 15-16 of the instant application, including B cells expressing immunoglobulins specific for antigens comprising a terminal alpha 2,6 linked sialic acid.

Applicant has argued in the context of a similar rejection that in order to anticipate the instant claims, the prior art must identically disclose or describe the claimed subject matter, and that the Office has recognized an analogous distinction between the prior art and methods of reducing a pro-tumor immune response, as recited in US Pat. No. 6,224,866.

However, it is noted that the CAFC recently held in Bristol-Myers Squibb Co. v. Ben Venue Laboratories Inc., 58 USPQ2d 1508 (CA FC 2001) that when a claimed process is not directed to a new use, consists of the same steps described in a prior art reference, and the newly discovered results of the known process directed to the same purpose are inherent, the process is not patentable.

In the instant case, the method comprises the same step of administering an antibody that depletes B cells to treat the same patient population, those suffering from MS. Depletion of B cells would necessarily result in the reduction of a pro-MS immune response.

The teachings of the reference thus anticipate the instant invention.

8. Claims 1-2, 4-5, 10-11, 13-15 and 17 are rejected under 35 U.S.C. 102(e) as being anticipated by Aruffo et al (US Pat. No. 6,051,228, see entire document).

Aruffo et al. teach a method of treating multiple sclerosis (MS) by administering a chimeric antibody to the CD40 antigen (see entire document, e.g., columns 21-22 and in particular column 21 at lines 25-31). Aruffo et al. teach that CD40 is a B cell determinant expressed on B cells (e.g., column 1 at lines 14-22, and that antibody to CD40 depletes B cells when administered in vivo (e.g., column 9 at lines 46 and column 12 at lines 37-55). Aruffo et al. teach that the anti-CD40 antibody is administered as a composition comprising a pharmaceutically acceptable carrier (e.g., columns 21 to 22). Aruffo et al. teach that the compositions comprising the anti-CD40 antibody may be administered intravenously, or by other parenteral routes (e.g., column 21 at lines 32-36).

Depleting B cells with an anti-CD40 antibody *in vivo* would also inherently deplete mature and memory B cells, $CD19^+sTn^+$ B cells, $CD19^+CD21^+sTn^+$ B cells and $CD19^+CD5^+sTn^+$ B cells, including nonmalignant B cells. Finally, administering an anti-CD40 antibody to treat an individual suffering from MS would also inherently require that the antibody be administered in an amount effective to reduce the inflammation underlying the clinical manifestations of MS. Applicant is reminded that no more of the reference is required than that it sets forth the substance of the invention. The claimed functional limitations would be inherent properties of a method comprising administering an anti-CD40 antibody to an individual suffering from MS.

An individual suffering from multiple sclerosis would inherently have a pro-MS immune response, as defined on pages 15-16 of the instant application, including B cells expressing immunoglobulins specific for antigens comprising a terminal alpha 2,6 linked sialic acid.

Applicant has argued in the context of a similar rejection that in order to anticipate the instant claims, the prior art must identically disclose or describe the claimed subject matter, and that the Office has recognized an analogous distinction between the prior art and methods of reducing a pro-tumor immune response, as recited in US Pat. No. 6,224,866.

However, it is noted that the CAFC recently held in Bristol-Myers Squibb Co. v. Ben Venue Laboratories Inc., 58 USPQ2d 1508 (CA FC 2001) that when a claimed process is not directed to a new use, consists of the same steps described in a prior art reference, and the newly discovered results of the known process directed to the same purpose are inherent, the process is not patentable.

In the instant case, the method comprises the same step of administering an antibody that depletes B cells to treat the same patient population, those suffering from MS. Depletion of B cells would necessarily result in the reduction of a pro-MS immune response.

The teachings of the reference thus anticipate the instant invention.

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> *(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.*

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

10. In order to better address Applicant's arguments regarding the animal model of MS utilized by Genain et al., filed 924/01, the previous rejection of claims 1-17 under 35 U.S.C. 103(a) as being unpatentable over Turk et al. (US Pat. No. 5,958,409, or record) in view of Genain et al. (J Clin Invest 1995 96:2966-2974, of record) and Anderson et al. (US Pat. No. 5,776,456, IDS) is withdrawn in favor of the rejection set forth below.

11. Claims 1-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Turk et al. (US Pat. No. 5,958,409, or record) in view of Genain and Hauser (J. Mol. Med. 1997 75:187-197) and Anderson et al. (US Pat. No. 5,776,456, IDS).

Applicant's arguments, filed 9/24/01, as they apply to the instant rejection have been fully considered but have not been found convincing, as addressed below.

The claims are drawn to a method for reducing a pro-MS immune response, or for treating an individual having MS and a pro-MS immune response or a pro-MS immune response by administering an affinity ligand for a B cell determinant that depletes the targeted nonmalignant B cells, including an affinity ligand that is a chimeric anti-CD20 antibody.

Turk et al. teach and claim a method for treating multiple sclerosis (MS) by administering a therapeutically effective amount of a composition comprising an affinity ligand that is a chimeric antibody that binds the cytokine TNF-α (see entire document, including claims).
Turk et al. also teach

administering a composition comprising the chimeric antibody in combination with a pharmaceutically acceptable carrier (e.g., claim 3 and bridging paragraph of columns 4 and 5);

administering the composition

in a site-directed method directly to the central nervous system (e.g., claims 4 and 5), or

by intravenous (i.e., parenteral) injection (e.g. column 7, especially lines 1-15);

further administering an additional component including a chemotherapeutic, anti-inflammatory, or cytolytic agent (e.g., column 7, especially lines 50-56).

Turk et al. also teach that although TNF-α has been implicated as an important effector molecule in MS, other mediators are also important in producing the CNS pathology observed in MS (e.g. columns 2-3 and 7-8). Turk et al. exemplify treatment of EAE (an animal model of MS), in the chronic-relapsing mouse model developed in Biozzi AB/H mice (see Examples, e.g., description of mouse model at column 9).

Turk et al. do not teach administering a composition comprising an affinity ligand that binds a determinant on B cells and effects B cells depletion, such as a chimeric anti-CD20 antibody.

Genain and Hauser teach that production of the fully demyelinating lesion of MS involves the interaction of encephalitogenic T cells, proinflammatory cytokines such as TNF-α, and pathogenic antibody (see entire document, e.g., as summarized in the Discussion on page 195). Genain and Hauser review the contribution of the many animals EAE models of MS and their invaluable contributions to understanding the basic immunological mechanisms that underlie autoimmune inflammatory disease of the nervous system (see entire document, e.g., "Introduction").

Genain and Hauser note, however, that the previously established EAE models of MS have failed to provide a reliable indication that a therapeutic successful in EAE will also be successful in the treatment of MS. Genain and Hauser further discuss that important differences exist between previously established models of EAE and MS in terms of pathology, and that in forms of acute EAE inflammation predominates over demyelination, whereas acute demyelination is the pathological hallmark of the early MS lesion (e.g., page 188, left column).

Genain and Hauser present a marmoset model of MS and discuss the advantages of the marmoset model compared to the more widely used rodent models, noting in particular that the marmoset model is novel compared to the rodent models because it develops a relapsing-remitting form of EAE that is characterized clinically by moderate signs of neurological dysfunction and pathologically by early and prominent demyelination accompanied by macrophage infiltration and gliosis, all features of human MS (see especially pages 188-189).

Genain and Hauser also teach that in the marmoset model, like some (but not all rodent models), demyelinating EAE occurs when encephalitogenic T cells act in synergy with pathogenic antibodies (see especially page 188, rt column top and page 193-194). Genain and Hauser conclude that the demonstration of an antibody-mediated component for CNS autoimmune disease, both in the newly developed marmoset as well as certain rodent models, have fundamental implications for the design of future therapies in human MS (page 194, paragraph bridging columns).

Genain and Hauser summarize in Figure 6 that the pathogenesis of the MS-like lesions in the marmoset involve both inflammation involving a T cell component, and a demyelination involving antibody. One of ordinary skill in the art would immediately recognize in view of the teachings of Genain and Hauser that B cells, which were well known in the art to be the source of antibody, thus represent a therapeutic target for the treatment of MS.

Anderson et al. teach the production of a chimeric anti-CD20 antibody and the use of this antibody to deplete nonmalignant B cells *in vivo* (see entire document, especially Examples II and III on pages 27-page 37). Anderson et al. also teach that CD20 is expressed early in B cell development and remains until plasma cell differentiation (e.g., page 8, 2nd full paragraph).

Given these teachings, the ordinary artisan at the time the invention was made would have been motivated to combine or substitute a method of B cell depletion to reduce or eliminate autoantibody production with the method of treating MS taught by Turk et al. Turk et al. teach using an anti-inflammatory anti-TNF-α chimeric antibody in combination therapies that target other aspects of the MS autoimmune process. Genain and Hauser clearly identify antibodies to be an important component of pathogenesis in the marmoset model, and note that similar findings have been observed in some of the rodent models.

The Examiner notes that the Biozzi AB/H mice, which are the model system used by Turk et al., were known in the art to develop chronic-relapsing, rather than acute, EAE; and further notes that Biozzi AB/H (i.e., Biozzi AntiBody/High) mice were known in the art to be more susceptible to EAE induction than Biozzi AB/L (i.e., Biozzi AntiBody/Low) mice, as referenced in the teachings of Turk et al. at column 9, lines 45-51.

Given the clear direction provided by Genain and Hauser that antibody is central to mediating the demyelination found in marmoset EAE, and possibly some rodent models, and that the marmoset EAE model is novel in that it is a particularly representative animal model of MS in terms of the pathology that develops; the ordinary artisan would have had a reasonable expectation that depletion of the B cells that produce the pathogenic antibodies would reduce the demyelination associated with MS and certain EAE models.

Anderson et al. teach that a chimeric anti-CD20 antibody efficiently depletes B cells *in vivo*; and given the expression of CD20 throughout B cell development the ordinary artisan would have reasonably expected that anti-CD20 therapy would deplete mature and memory B cells, $CD19^+sTn^+$ B cells, $CD19^+CD21^+sTn^+$ B cells and $CD19^+CD5^+sTn^+$ B cells, including nonmalignant B cells when administered to an individual with MS. Irrespective of whether or not a "pro-MS immune response" as defined in the specification on pages 15-16 was tested for in individuals with MS, targeting the pan B cell antigen CD20 would lead to a depletion of B cells irrespective of Ig specificity, and so would necessarily deplete B cells expressing immunoglobulins specific for antigens comprising a terminal alpha 2,6 linked sialic acid.

Thus given the teachings of Genain and Hauser identifying antibody produced by B cells as a primary therapeutic target in MS, the teachings of Anderson et al. that a chimeric anti-CD20 antibody depletes B cells in vivo, and the teachings of Turk et al. that a chimeric anti-TNFα antibody should be used in combination with other agents that target other aspects of the MS autoimmune process; the ordinary artisan at the time the invention was made would have been motivated to substitute or combine the chimeric anti-CD20 antibody of Anderson et al. with the chimeric anti-TNFα antibody of Turk et al. in a method of treating individuals with MS, including administering the combination of antibodies both intravenously (i.e., parenteral) and intrathecally (i.e., in a site-directed manner by delivery into an access that directly supplies the central nervous system). The ordinary artisan at the time the invention was made would have been motivated in particular to combine the antibodies of Anderson et al. and Turk et al. to target multiple components of the MS immune response with an expectation that the combined therapy would be more efficacious than the single therapy approach. Alternatively, the ordinary artisan would administer only the chimeric anti-CD20 antibody of Anderson et al. during phases of remission in order to maintain depletion of B cells. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

In the context of a similar rejection of record, Applicant has presented several references to support the position that one of ordinary skill in the art at the time the invention was made would not have recognized the role of B cells in MS. Applicant cites Rudick et al. (New Engl. J. Med. 1997; 337:1604-1611) for support that the ordinary artisan recognized neither B cells, nor a pro-MS response, as an established target for therapy of MS since these therapies were not employed clinically. The Examiner acknowledges that such therapies were not employed in the clinic at the time the invention was made; however, absence of clinical therapies targeting B cells at the time the invention was made does not negate the teachings of the cited references that the antibodies produced by B cells are of clinical significance since they are associated at least in the marmoset model with demyelination.

Applicant also provides the Hjelmstrom et al. (J. Immunol. 1998; 161:4480-4483) and Wolf et al. (J. Exp. Med. 1996; 184:2271-2278) references which show that B cells and their antibody products are not essential for the induction of demyelination in EAE mouse models of MS because B cell deficient mice can still develop EAE with demyelination. Applicant argues that the ordinary artisan recognized these mouse models of EAE to be the standard experimental model of MS, and contrasts the observations in mouse EAE with the teaching of Genain et al. cited by the Examiner.

That mice can develop EAE with some demyelination in the absence of B cells in not disputed by the Examiner. However, the Examiner does not agree that mice represent a standardized model of EAE that precludes the acceptance by the ordinary artisan of findings in other models of EAE with respect to the pathogenesis of human MS. Genain and Hauser do acknowledge that mouse models of EAE have provided valuable information regarding the antigens involved (e.g. Introduction).

However, as discussed supra Genain and Hauser note that pathologically, the marmoset is novel in that it better represents the pathological features of human MS. Hjelmstrom et al. examine a mouse model of the chronic-sustained form of EAE, which is distinct from the chronic-relapsing model studied by Turk et al. and distinct from the chronic-relapsing nature of EAE observed in the marmoset model. Similarly, the mouse EAE model employed by Wolf et al. does not suffer from a chronic-relapsing course, but instead spontaneously recovers. Thus the Examiner maintains that one of ordinary skill in the art would not consider these mouse studies to be a teaching away from role of B cells in MS because the data in different models conflict, and the models that better represent the pathology of human MS clearly indicate a role for antibody in the demyelinating pathology observed in MS and thus provide a reasonable expectation that depleting B cells would be therapeutically beneficial in treating MS.

Applicant also argues that MOG autoantibodies are not specific to MS and cites Karni et al. (Arch. Neurol. 1999; 56:311-315) for support that antibodies to MOG are observed in other neurological disease.

The Examiner notes that while MOG and anti-MOG antibodies can be utilized to induce EAE in the marmoset, as well as in other EAE models; neither in this rejection or the previous rejection of record was any reliance made upon the particular antigen. Further, while immunization with MOG and anti-MOG antibody transfer have been used in EAE models, including the marmoset; Genain and Hauser clearly recognize that multiple antigens are involved (see e.g., Figure 6 and pages 191-195). Finally, that anti-MOG may be present in other patients with neurological diseases does not negate a role for MOG in the demyelination observed in MS, as it was well accepted in the art, as taught supra by both Turk et al. and Genain and Hauser that MS involved the interaction of multiple immunological mediators.

Thus the Examiner acknowledges MS is a complicated autoimmune disease involving the interaction of not only B cell products, but also T cells, macrophages and cytokines such as TNF-a; and that there are multiple, and sometimes conflicting models of MS. However, given the teachings of the references cited, the ordinary artisan at the time the invention was made would have found it obvious to deplete B cells as one means of reducing the pathology of MS and in depleting B cells would have necessarily reduced a pro-MS response. Therefore, the Examiner maintains that the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the teachings of the references relied upon in the rejection set forth.

12. Claims 6-7 and 9 are rejected under 35 U.S.C. 103(a) as being unpatentable over either Hale et al (US Pat. No. 6,120,766) or Aruffo et al (US Pat. No. 6,051,228) in view of Turk et al. (US Pat. No. 5,958,409, or record).

The claims are drawn to a site direct method of reducing a pro-MS immune response in an individual by administering a composition comprising an affinity ligand of a B cell determinant to the individual into an access that directly supplies the central nervous tissue.

Hale et al. and Aruffo et al. have been discussed supra and each teach a method comprising administering a composition comprising an affinity ligand of a B cell determinant to treat an individual suffering from MS.

Neither Hale et al. or Aruffo et al. teach administering the composition into an access that directly supplies the central nervous tissue.

However, Turk et al. who have also been discussed supra, teach in the context of treating MS, a disease of the central nervous system, the administration of therapeutic compositions into an access that directly supplies the central nervous tissue (i.e., intrathecally, as recited in claim 5 of Turk et al. and at column 7, lines 1-15).

Thus it would have been obvious to the ordinary artisan at the time the invention was made to administer the compositions taught by either of Hale et al. or Aruffo et al. in a site-directed manner directly into an access that directly supplies the central nervous tissue. The ordinary artisan would have been motivated to select a site-directed administration protocol in order to ensure access of the administered composition to the central nervous system undergoing the disease, particularly in view of the art recognized blood-brain barrier. Given the established nature of intrathecal administration, the ordinary artisan at the time the invention was made would have had a reasonable expectation that a site-directed administration of the compositions of Hale et al. or Aruffo et al. could have also been employed in the method taught. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

13. No claim is allowed.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jessica H. Roark, whose telephone number is (703) 605-1209. The examiner can normally be reached Monday to Friday, 8:00 to 4:30. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached at (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.

Jessica Roark, Ph.D.
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July 1, 2002

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7/1/02